Hepatitis A
Hepatitis E
Typhoid Fever

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Overview

- Commonalities
  - similar presentations
  - in developing countries
  - associated with poor sanitation/hygiene
  - fecal-oral transmission
  - typically acute and self-limited
- Differences
  - bacteria vs. viral
  - therapy
  - complications of infection
  - preventative measures (vaccines)

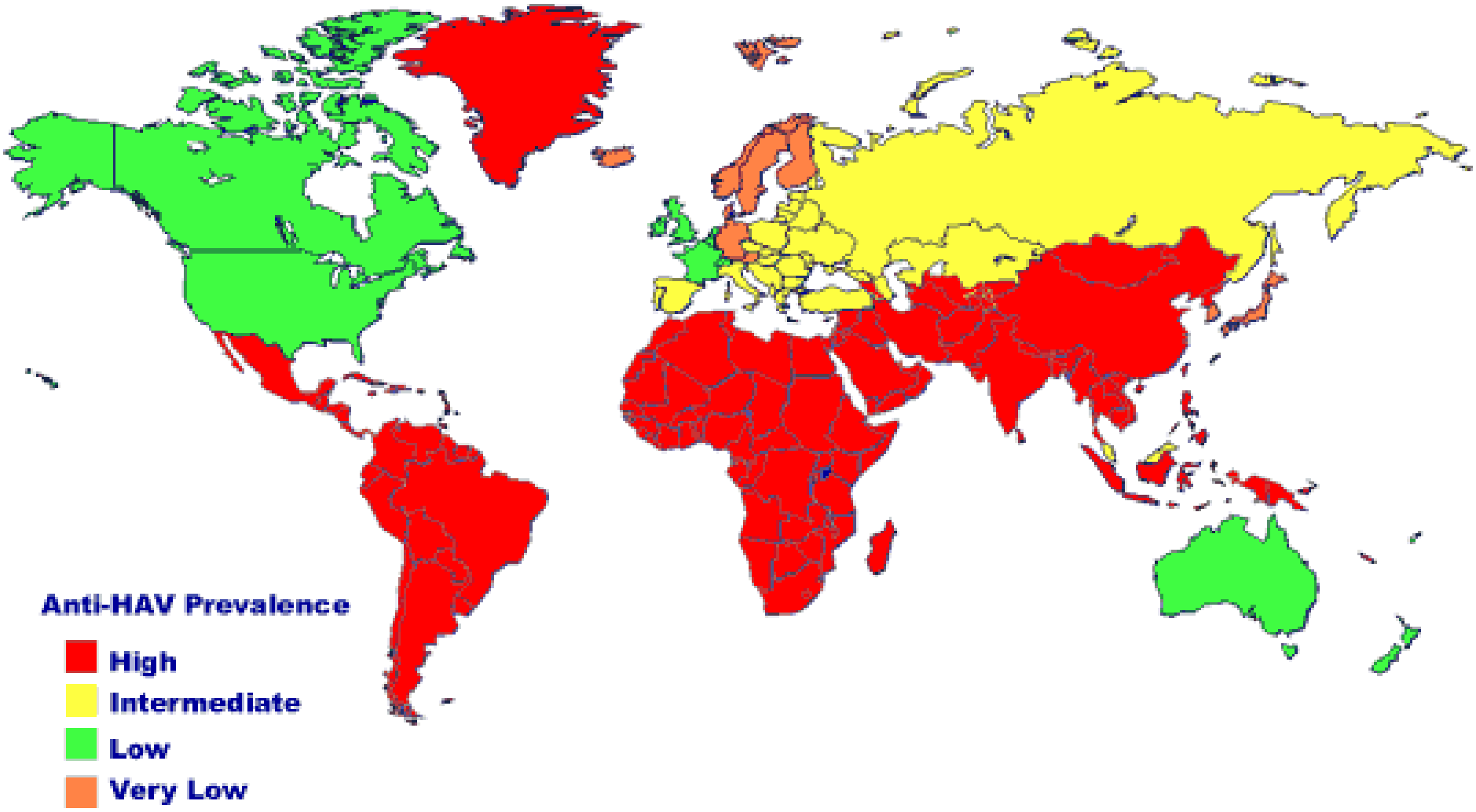
Viral Hepatitides

- Hepatitis A and E
  - transmitted fecal oral
  - typically no chronic disease issues
- Hepatitis B, C, and D
  - transmitted via blood and blood-derived body fluid exposure
  - chronic disease may develop

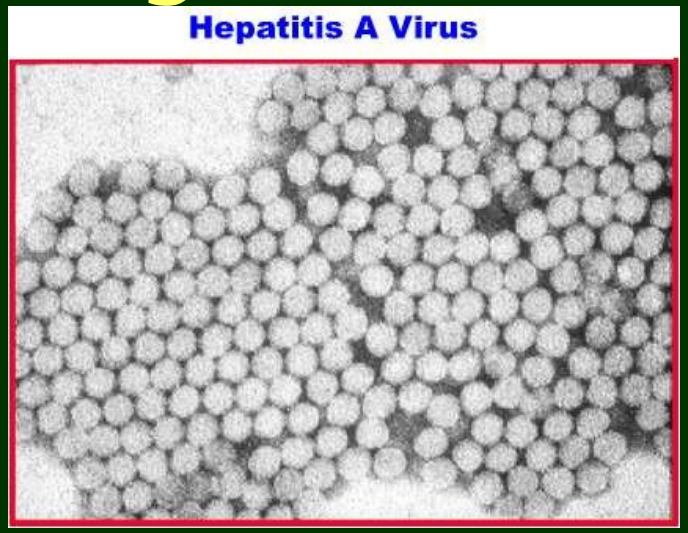
Hepatitis A

- Background
  - Also called “infectious hepatitis”
  - most common viral hepatitis in 2001 in U.S.
  - occurs worldwide with highest prevalence in Central/South America, Africa, India, Middle East, Asia
  - Affects 1.4 million people worldwide annually
  - 10,600 cases in U.S. in 2001
    - decreasing incidence of infection with childhood immunization
    - rates have been shown to vary with time
- Most prevalent in areas of low socioeconomic status and poor sanitation

Geographic Distribution of HAV Infection



Hepatitis A-Pathogenesis



- RNA virus
- Spread by fecal-oral transmission
- Occurs sporadically or i epidemics
  - frozen strawberry associated epidemic
  - contaminated food from infected food handlers or contaminated water
  - Areas of poor sanitation have high incidence in young children with asymptomatic infection, and fewer adult cases
  - Better sanitation, less kid cases, more serious adult cases

Recent Outbreak

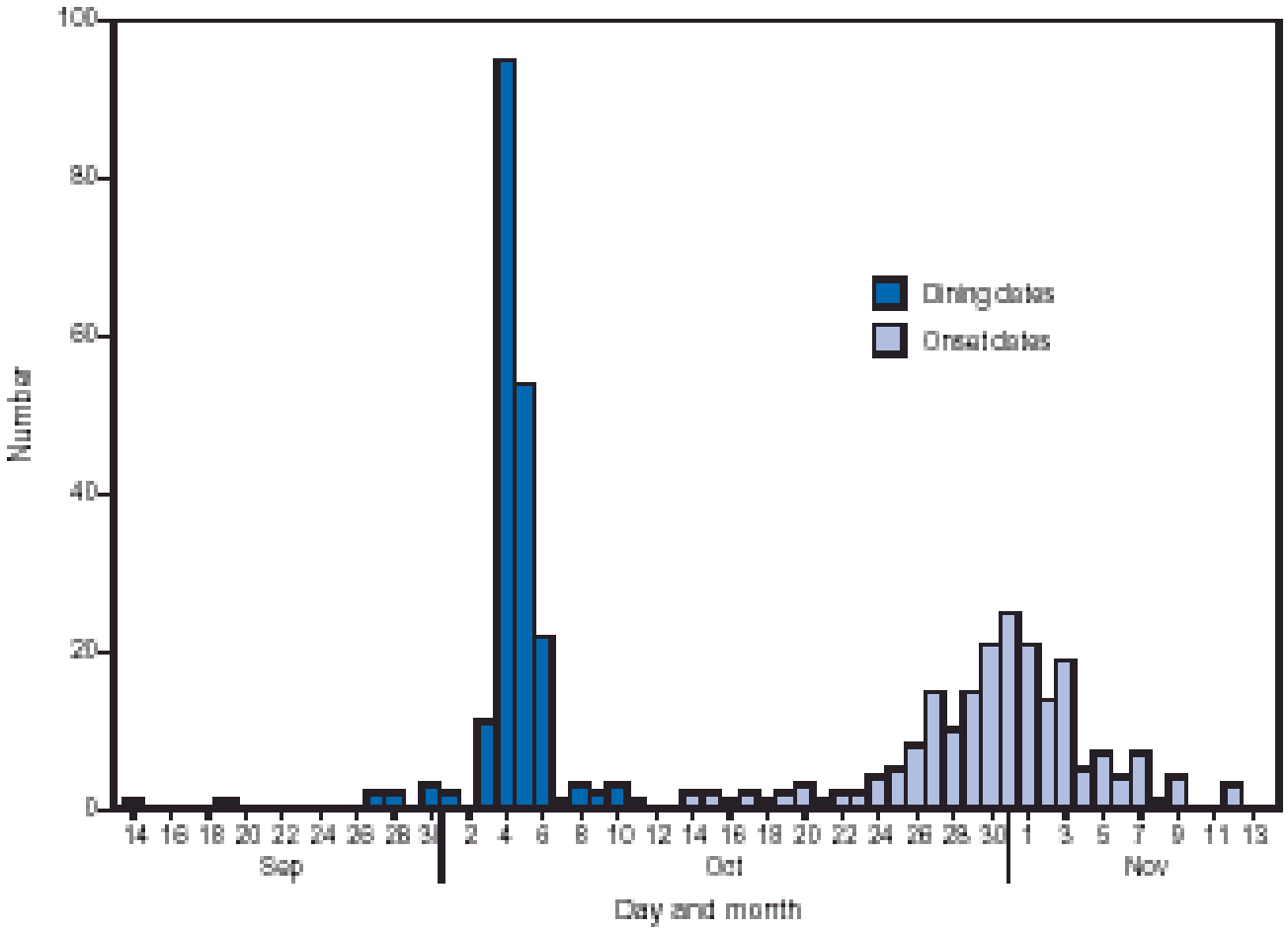
- Pennsylvania restaurant
- 640 people diagnosed with Hep A, Oct/Nov ‘03
  - 13 restaurant food service employees
  - 75 from six other states who dined at this restaurant
  - 3 died
- Outbreak associated with contaminated green onions from Mexico
- Lawsuits

Hepatitis A-Symptoms

- Usually a self-limited, ACUTE, illness
- Rarely fulminant hepatic failure
- Sx will vary with age
- Incubation is 15-50 days (average of 30 days)

- PA outbreak
  - date of onset 14 Oct - 12 Nov
  - date of exposure 14 Sept - 17 Oct (3-6 Oct)

FIGURE. Number of hepatitis A cases*, by date of eating at Restaurant A and illness onset — Monaca, Pennsylvania, 2003



* N = 206. Excludes one case-patient whose illness onset date was not available. Dining dates for three persons who ate at Restaurant A on October 15 (n = one) and October 17 (n = two) are not shown.

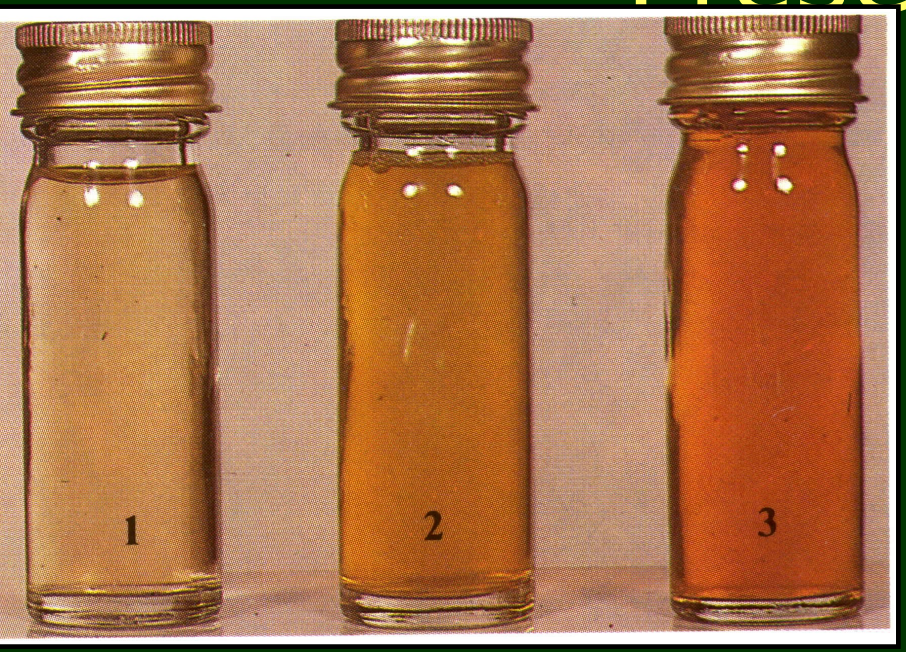
MMWR 52:1155-1157. 28 Nov 2003

Hepatitis A-Clinical Presentation

- Classic HAV infection (80% of symptomatic patients)
  - usually asymptomatic in children
  - adults can have a flu-like illness to hepatic failure
  - fatigue, malaise, nausea/vomiting, anorexia, fever, RUQ pain
  - loose taste for tobacco
  - develop dark urine, gray stools, jaundice, pruritus
- Signs
  - hepatosplenomegaly, tender liver, jaundice

Hepatitis A-Clinical Presentation

Hepatitis A-Clinical Presentation



normal cholestasis: Cirrhosis:
conjugat bili urobili
green-yelloworange

Stools pale due to obstruction of biliary excretion of bilirubin pigments

Hepatitis A-Clinical Presentation

- Relapsing Hep A infection (4-20%)
  - 2 or more bouts of acute HAV infection over 6-10 weeks
  - sx-free intervals, progressive bouts are milder
- Cholestatic Hep A infection (10%)
  - prolonged course over months
  - fever with marked pruritus and jaundice
  - bilirubin remains elevated with other liver associate enzymes normal

Hepatitis A-Diagnosis

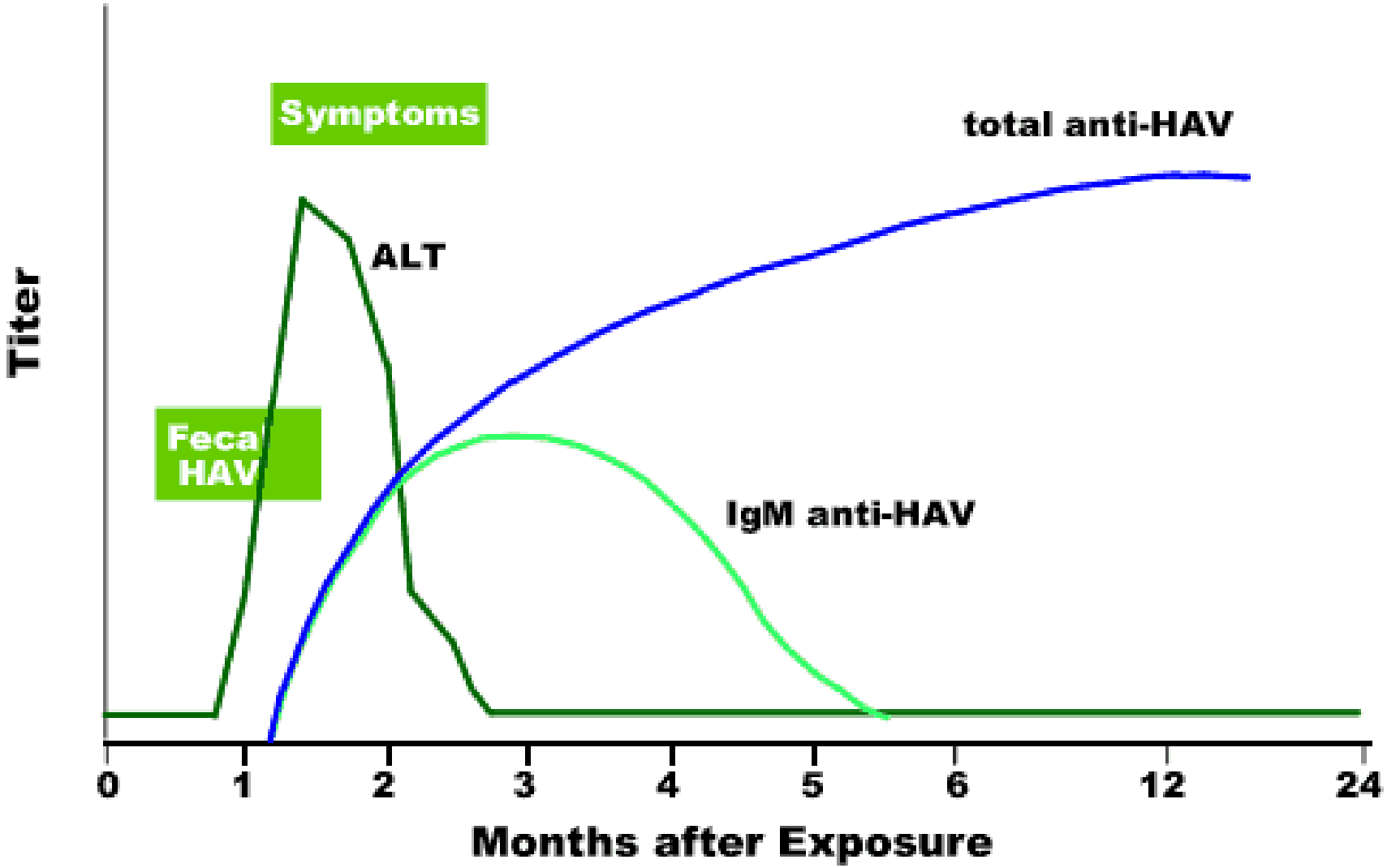
- Clinical syndrome consistent with HAV infection
- Elevated Liver associated enzymes
  - Average ALT=2000, Average AST=1500
  - LAE elevation does not correlate with severity of disease or prognosis

Hepatitis A-Diagnosis

- Detect Anti-HAV AB in serum
  - serum anti-HAV IgM is the gold standard
    - IgM is elevated at 1-2 weeks after exposure, and persists for 3-6 months
  - serum anti-HAV IgG infers prior infection or vaccination
    - IgG is protective (lifelong?)
    - detectable at 5-6 weeks after exposure, persists for decades
- Prolonged PT can be a sign of impending liver failure.

Hepatitis A Virus Infection

Typical Serologic Course



Hepatitis A-Diagnosis

- Liver biopsy is not needed to make the diagnosis.

- HAV virus is shed in the stool 2 weeks prior to the onset of jaundice, and one week after
  - may be shed longer in children and infants
  - in infants can be up to six months after onset of sx
  - typically in adults, only for one week after the onset of sx

Hepatitis A-Treatment

- Acute HAV infection is self-limited
- Treatment is supportive
  - treat dehydration, coagulopathy, encephalopathy, if elderly, or have some other chronic liver disease
  - avoid alcohol and other hepatotoxins (acetaminophen <2gm/day)
- Steroids considered for prolonged cholestatic form of HAV
  - no evidence that this improves outcome
  - may shorten duration of illness

Fulminant Hepatitis A

- 0.35% of adult cases
- Danger signs include excitability, irritability, insomnia, confusion, severe vomiting
- Heralded by worsening jaundice, encephalopathy, and prolonged PT (one week 55%, one month 90%)
- Patients at risk are elderly or have chronic liver disease
- Fatality rate of 2% (others 0.3%, 1.8% if age>50)
- Early referral for liver transplant is required

Hepatitis A-Prevention

- Improve sanitary conditions, hand washing, avoidance of contaminated food/water sources.
- Passive immunization
- Active immunization

Hepatitis A-Prevention

- Passive immunization
  - Immune serum globulin (sterile preparation of concentrated AB made from pooled human plasma)
  - IGIM used for hep A prevention
  - not to be given with live attenuated virus vaccines (MMR, VZV, yellow fever)

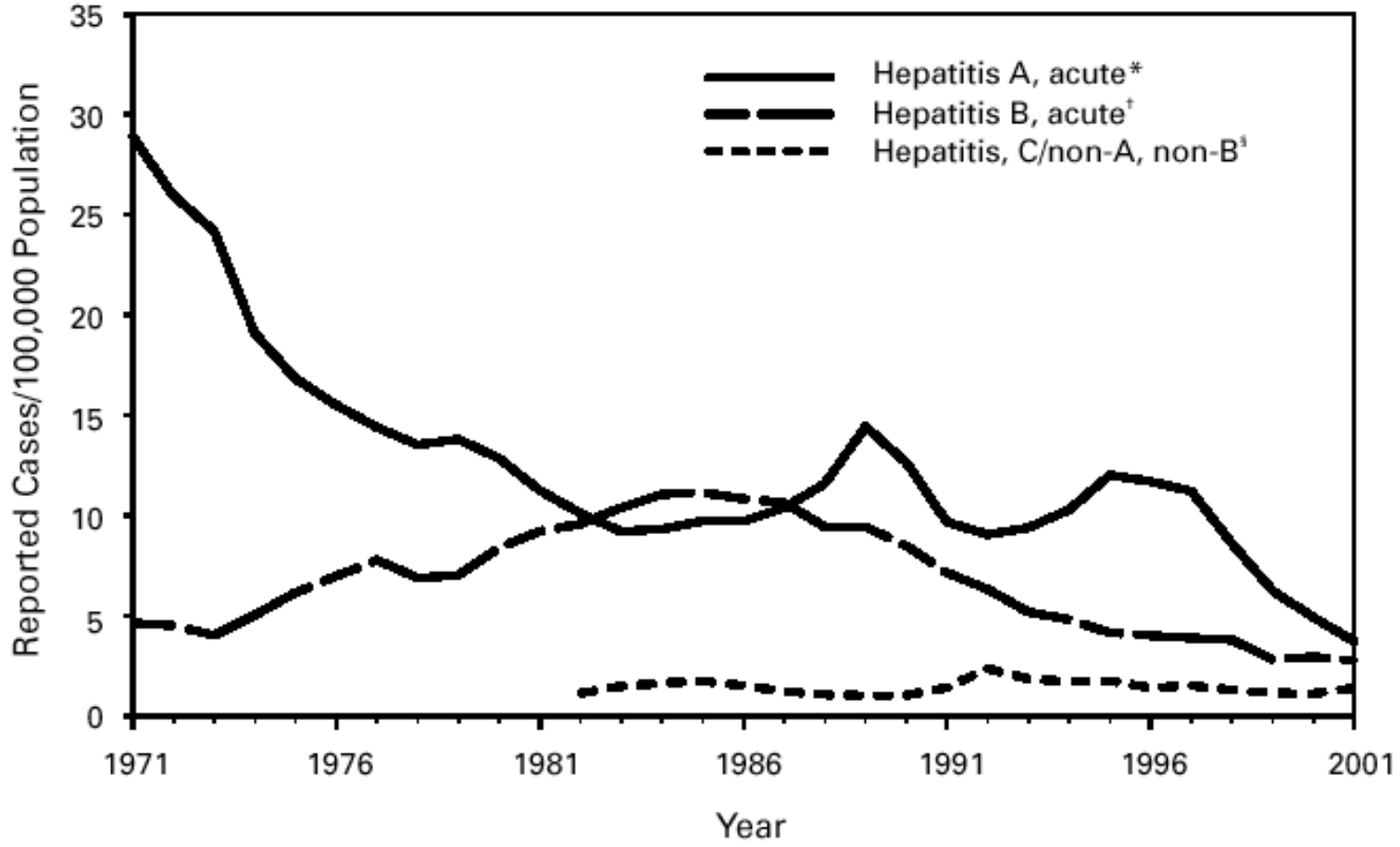
Active immunization

- Two HAV vaccines approved for use
  - HAVRIX and VAQTA, both formalin inactivated
  - both are safe and efficacious
  - protective AB after one month (~90%) and 7 months (~100%)
  - two doses; zero and six months
  - protects 5-10 years (longer?)
  - can give with ISG as HAV vaccine is an inactivated virus

Hepatitis A-Prevention

- HAV vaccine--give to the following
  - kids in areas of the U.S. with rates of infection 2X national average (Native Americans, Native Alaskans)
  - travelers to areas endemic for HAV
    - your military population
  - homosexual males
  - patients with clotting disorders
  - illicit drug users
  - lab techs in HAV research labs
  - patients with chronic liver disease due to HBV, HCV, or before liver transplant

HEPATITIS. Reported cases per 100,000 population, by year — United States, 1971–2001



*Hepatitis A vaccine was first licensed in 1995.
† Hepatitis B vaccine was first licensed in June 1982.
§ An anti-HCV (hepatitis C virus) antibody test first became available in May 1990.

In 2001, the hepatitis A rate was the lowest ever recorded. However, cyclic increases in hepatitis A have been observed approximately every 10 years, and thus rates could increase again. The incidence of hepatitis B continues to decline, but because of asymptomatic infections and underreporting, reported cases represent only a fraction of actual infections occurring (approximately 78,000 new infections in 2001). The trend in reported hepatitis C; non-A, non-B after 1990 is misleading because reported cases have included those based only on a positive laboratory test for anti-HCV, and most of these cases represent chronic HCV infection.

MMWR 50:1-108, 2 May 2003

Hepatitis A

TABLE 2. Burden of hepatitis A in states with average reported incidence of >=20 cases per 100,000 population -- 1987-1997*

State	Rate (per 100,000)	Cumulative average number of cases per year†	Cumulative percentage of cases	Cumulative percentage of U.S. population§
Arizona	48	1,852	7	2
Alaska	45	2,137	8	2
Oregon	40	3,297	12	3
New Mexico	40	3,916	14	4
Utah	33	4,519	16	5
Washington	30	6,007	21	7
Oklahoma	24	6,786	24	8
South Dakota	24	6,953	25	8
Idaho	21	7,172	26	9
Nevada	21	7,449	27	10
California	20	13,706	50	

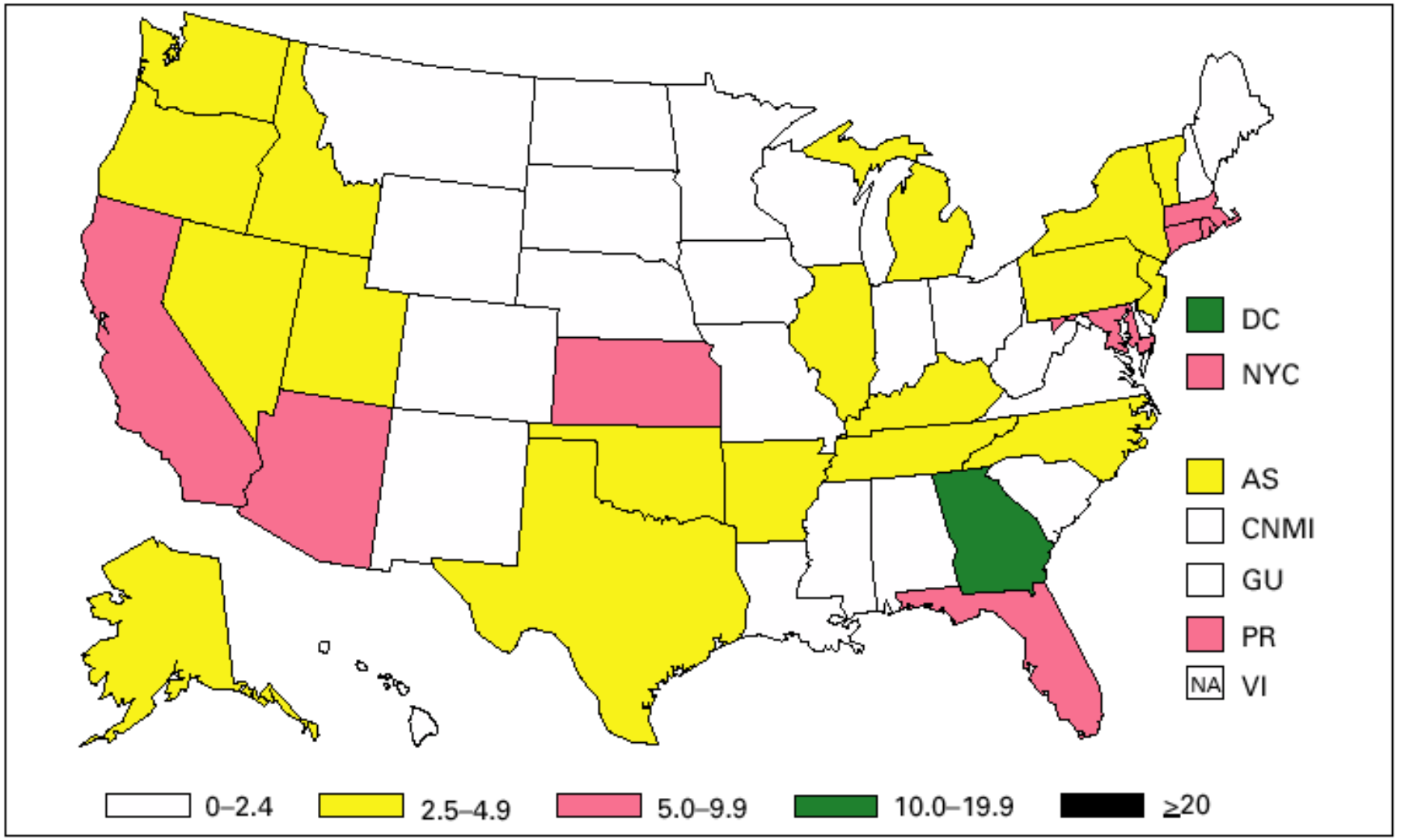
MMWR 48:1-37, 1 Oct 1999

TABLE 3. Burden of hepatitis A in states with average reported incidence of >=10 cases per 100,000 but <20 per 100,000 population -- 1987-1997*

State	Rate (per 100,000)	Cumulative average number of cases per year†	Cumulative percentage of cases	Cumulative percentage of U.S. population§
Missouri	19	1,000	4	2
Texas	16	3,881	14	9
Colorado	16	4,432	16	11
Arkansas	14	4,777	17	12
Montana	11	4,870	18	12
Wyoming	11	4,921	18	12

* United States reported disease incidence during 1987-1997 was 10.8 cases per 100,000 population.

HEPATITIS A. Reported cases per 100,000 population — United States and U.S. territories, 2001



Hepatitis A rates have declined in all regions of the United States, including the western states where rates have historically been higher than elsewhere in the country. Because hepatitis A rates vary from year to year with nationwide increases approximately every 10 years, further monitoring is needed to determine whether these rates will remain low.

MMWR 50:1-108, 2 May 2003

Hepatitis A

- Texas immunization requirements

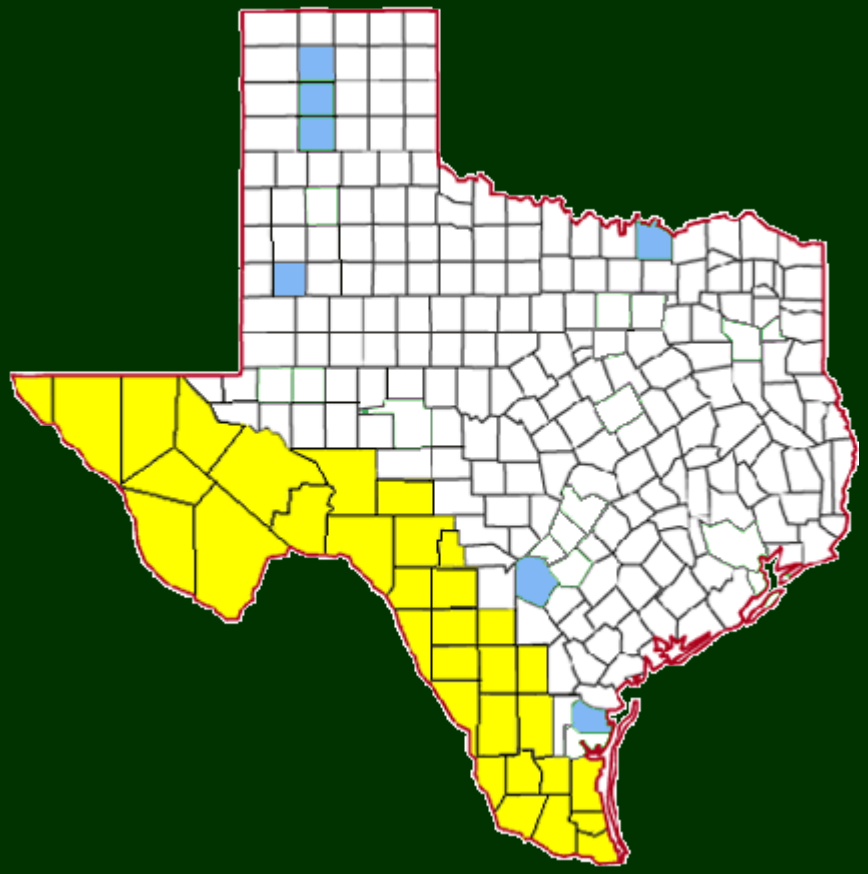
15 mos. through 4 years

Effective 8/1/03-7 counties in addition to 32 border counties, require hepatitis A vaccine.

2 years - One dose hepatitis A vaccine;
3 through 4 years - 2 doses of hepatitis A vaccine (1st dose on or after 2nd birthday)
Three doses polio vaccine
Four doses DTP/DTaP (Fourth dose not required until 18 months.)
One dose Hib vaccine on or after 15 months of age, unless a primary series and booster[g] have been completed
One dose MMR vaccine received on or after 1st birthday[b]
One dose of varicella vaccine received on or after 1st birthday[c]

Hepatitis A vaccine (selected counties)[d]:
2 years-One dose of hepatitis A vaccine;
3 through 4 years-Two doses of hepatitis A vaccine (1st dose on or after 2nd birthday

Hepatitis A



Original 32 Border Counties		As of August 1, 2003
• Brewster • Brooks • Cameron • Crockett • Culberson • Dimmitt • Duval • Edwards • El Paso • Frio • Hidalgo • Hudspeth • Jeff Davis • Jim Hogg • Kenedy • Kinney	• La Salle • Maverick • McMullen • Pecos • Presidio • Real • Reeves • Starr • Sutton • Terrell • Uvalde • Val Verde • Webb • Willacy • Zapata • Zavala	• Bexar • Grayson • Moore • Nueces • Potter • Randall • Terry

Hepatitis A Virus is the most common vaccine-preventable illness among

References

Viral Hepatitis A, in Control of Communicabel Diseases Manual, James Chin Editor, 17th ed, 2000.

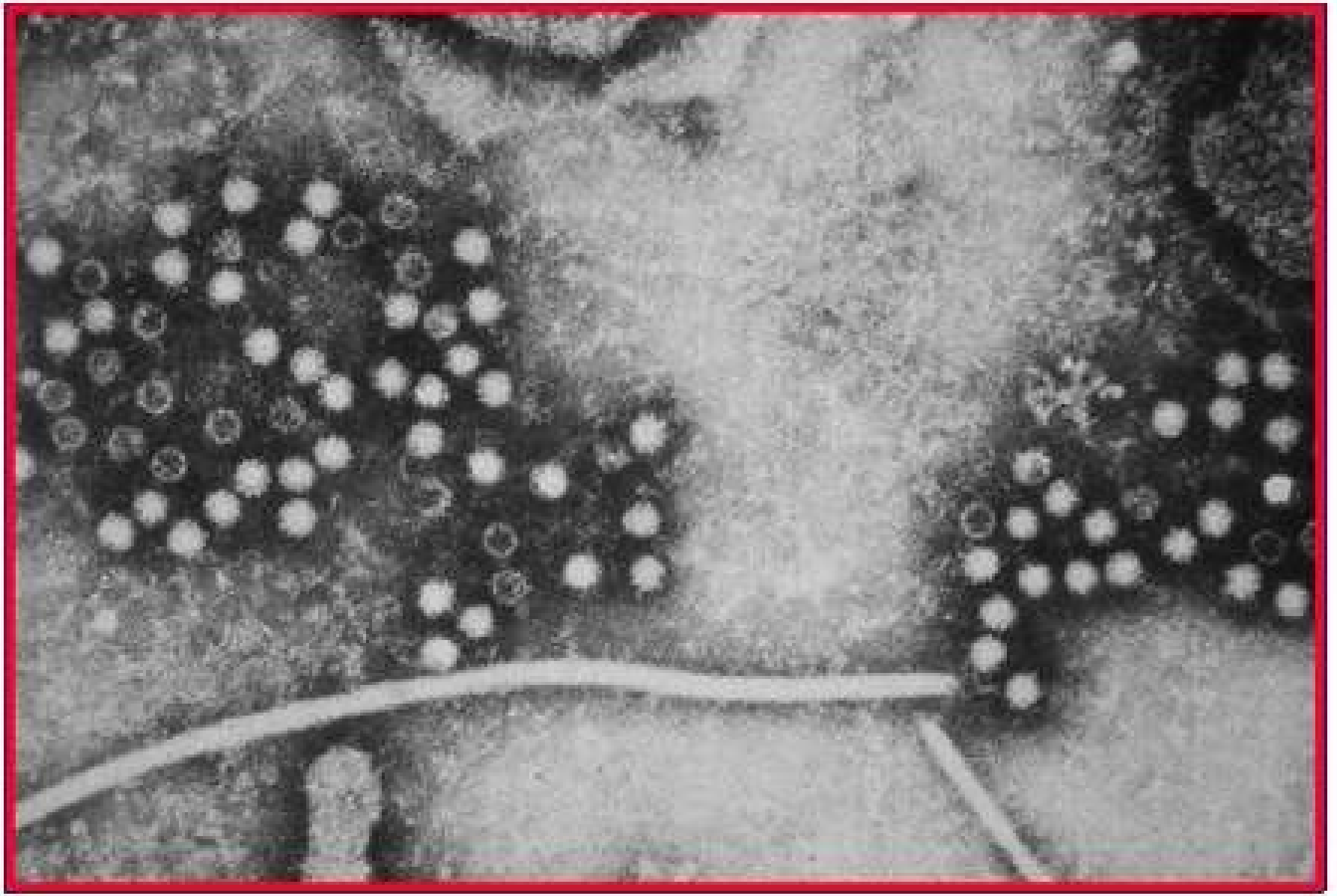
Stapleton JT. Host immune response to Hepatitis A virus. J Infect Dis. 1995;171(Sup1):S9-14.

Tong MJ, El-Farra NS, Grew MI. Clinical manifestations of Hepatitis A: Recent experience in a community teaching hospital. J Infect Dis. 1995:171(Sup1):S15-8.

Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR 48:1-37. 1 October 1999.

Hepatitis A Outbreak Associated with Green Onions at a Restaurant --- Monaca, Pennsylvania, 2003, MMWR 52:1155-1157, 28 Nov 2003.

Hepatitis E Virus

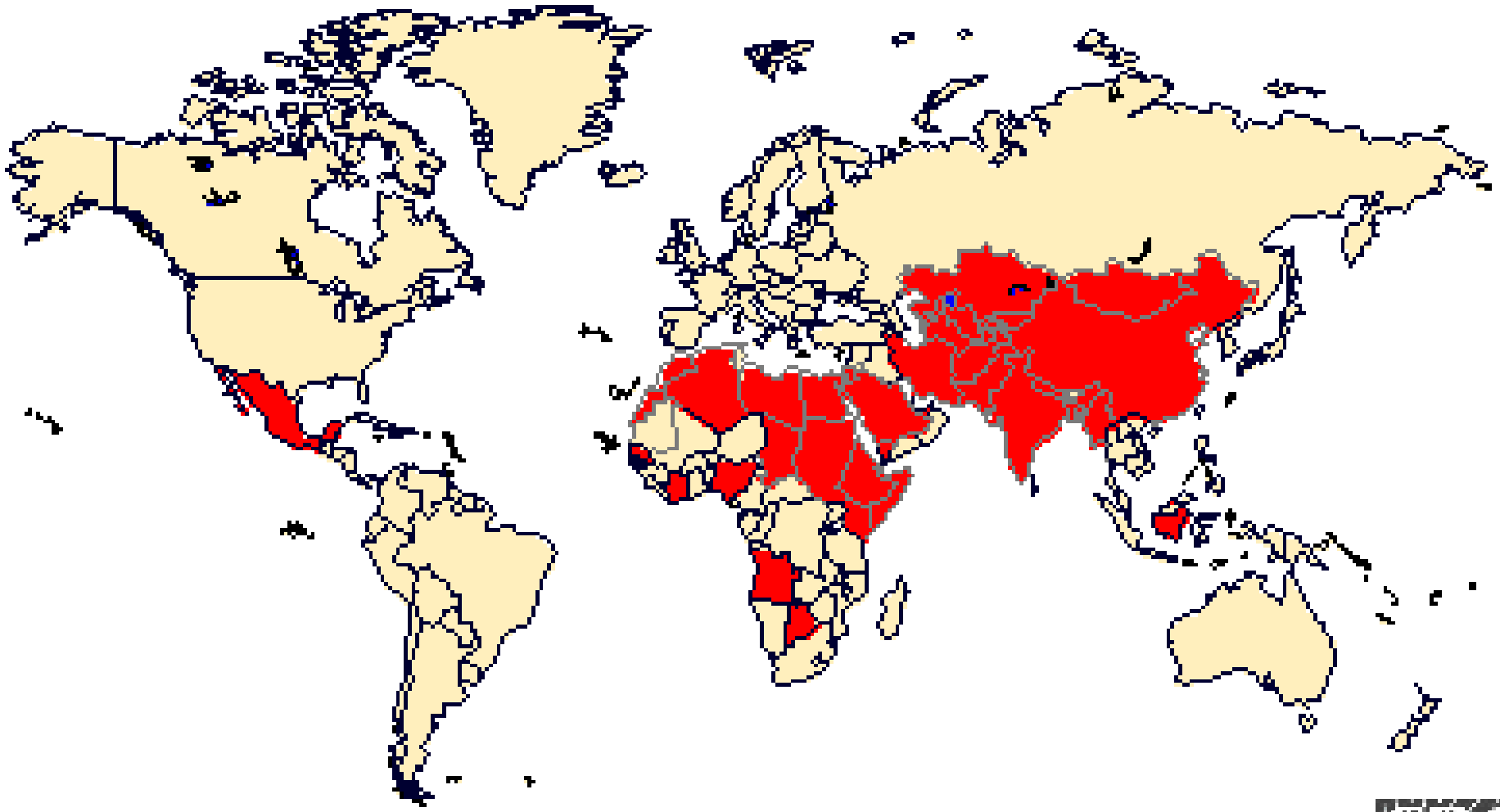


Hepatitis E Virus

- Enterically transmitted non-A, non-B hepatitis
- First identified in 1983
- Similar to HAV, but a different geographic distribution
  - HEV is restricted to tropical/sub-tropical developing countries
- RNA virus
- Transmitted fecal-oral
  - areas of poor sanitation, poor hygiene, and contaminated water supply
  - usually after heavy rains/flooding when water sources become contaminated

Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in > 25% of Sporadic Non-ABC Hepatitis



Hepatitis E- Pathogenesis/Epidemiology

- No person to person transmission
- No apparent parenteral or sexual transmission
- Cases occur from fecally contaminated water
- 2^{o} attack rates 1-2%, (HAV 50-70%)
- Causes epidemics of hepatitis (90% of epidemic hepatitis in India)
- HEV affects older children and adolescents and is a serious disease in this population in developing countries

Hepatitis E-Pathogenesis/Epidemiology

- Most significant impact is on pregnant women
  - mortality rate of 25%, especially in the 2nd and 3rd trimester

Hepatitis E-Clinical Presentation

- Self limited disease
- Similar to HAV infection
- No chronic sequelae of infection
- Incubation of 15-60 days, average 40 days

Hepatitis E-Clinical Presentation

- Acute Icteric Hepatitis most common
  - symptoms insidious in onset
  - flu-like sx, fever, malaise, abdominal pain, anorexia, nausea, aversion to tobacco, diarrhea
  - will develop dark urine, jaundice, and tender hepatosplenomegaly
  - symptoms last 1-4 weeks

Hepatitis E-Clinical Presentation

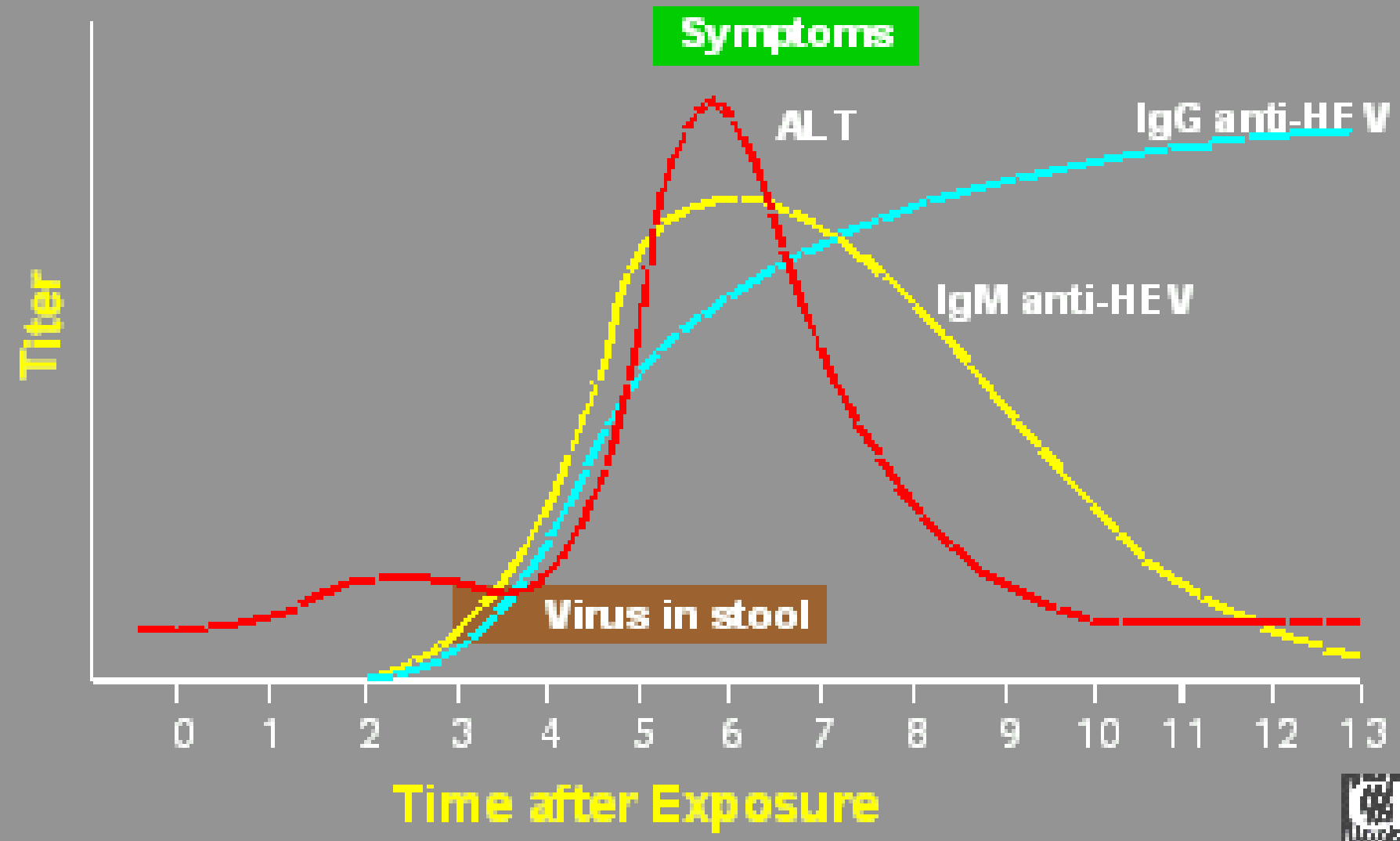
- Cholestatic hepatitis
  - presents with jaundice and itching
  - can last for 2-6 months, and will resolve spontaneously
- Anicteric hepatitis
  - very mild course
  - non-specific flu-like symptoms, no jaundice
- Fulminant, subacute, or late-onset hepatic failure
  - small proportion of infected individuals will have this
  - highest risk in pregnant females (25% mortality rate)
- Overall case-fatality rate of 0.5 to 4%

Hepatitis E-Diagnosis

- anti-HEV IgM present for 3-4 months, and gone by 4-5 months after exposure
- anti-HEV IgG presents within a week after IgM, and remains high for 4-5 years, but eventually diminishes over time
- HEV shed in stools one week prior to onset of symptoms, and persists as long as 2 weeks
- Liver associated enzymes can be elevated 10 days prior to onset of symptoms, and normal by 6 weeks

Hepatitis E Virus Infection

Typical Serological Course



Hepatitis E-Treatment/Prevention

- Treatment
  - Similar to HAV infection
  - Supportive therapy only
- Key to prevention is avoidance of contaminated water
  - drink from water of known purity, boiling water can help

Hepatitis E-Treatment/Prevention

- Passive immunization may be effective
  - commercially available ISG from endemic areas of unknown efficacy
  - because of large outbreaks seen in endemic areas, HEV IgG may not be fully protective or AB level may fall with time to decrease immunity
- Active immunization
  - no current vaccine, but under development

Typhoid Fever

Typhoid Fever

- Also known as “Enteric Fever”
- Caused by *Salmonella enterica serotype typhi* (or *Salmonella typhi*)
  - a human specific pathogen
- 16 million cases/year worldwide
- 600,000 deaths/year worldwide
- Passed by fecal-oral route, and with poor sanitation or contaminated water supply

Salmonella enterica serotype typhi

- Gram negative bacilli
- Enteric fever also caused by *S. paratyphi* A and B
  - overall 7.4% cases from non-typhoidal (most in U.S.)
- Low infectious dose
  - 10^3 usually causes disease
  - volunteer studies
  - lower infectious dose with higher stomach pH due to PPI or H2 blockers

Non-typhoidal *Salmonella* infection

- Infection with non-typhoidal *Salmonella* gives a mild self-limited gastroenteritis
- Nausea, vomiting, and diarrhea within 6-48 hours of ingestion
  - stool is loose, of moderate volume, and without blood
  - rarely can be large volume and watery
- Diarrhea is self-limited, lasts for 3-7 days

Typhoid Fever-Clinical Presentation

- Febrile illness occurs 5-21 days after ingestion
- Classic presentation--FEVER and ABDOMINAL PAIN
  - Asymptomatic 7-14 days after ingestion
  - 1st week--rising, sustained fever, malaise
  - 2nd week--abdominal pain and rash (rose spots on trunk and abdomen, occurs in 5-30% of cases)
  - 3rd week--hepatosplenomegaly
- Will slowly resolve over weeks to months, or can progress to a more serious presentation

Typhoid Fever-Clinical Presentation

Typhoid Fever-Clinical Presentation

- Classic presentation not the norm however
- May have diarrhea or constipation along with non-specific symptoms prior to the onset of fever
  - chills, diaphoresis, headache, anorexia, cough, weakness, sore throat, dizziness, and muscle pain
  - 5-10% with psychosis and confusion--picking at bedclothes and imaginary objects
  - “muttering delirium”
- Exam may reveal a relative bradycardia (pulse-temperature dissociation)

Typhoid Fever-Diagnosis

- Isolate the causative organism
  - Blood culture
  - Stool culture
  - Bone marrow culture
  - culture of rose spots
  - string test of duodenal secretions
- Serologic tests may not be helpful, and just prove prior infection
  - Widal's Test--detects AB to *S. typhi* antigen
- Labs may show anemia, leukopenia, or leukocytosis
  - abnormal liver associated enzymes, but may not be as high as with other viral hepatitides

Typhoid Fever--Therapy

- Careful of resistance
- Empiric therapy for Typhoid fever
  - outside the U.S. chloramphenicol is primarily used
  - quinolones or 3rd generation cephalosporins
  - decreased susceptibility to Cipro has been reported in India and Vietnam
- Regimens
  - Ciprofloxacin 500 mg PO BID for 7-10 days
  - Ceftriaxone 2-3 gm IV QD for 7-14 days
  - Alternate is Azithromycin 1 gm PO, then 500 mg PO QD for 7-14 days

Typhoid Fever--Therapy

- For severe typhoid fever (characterized by delirium, obtundation, stupor, or coma)
  - Expert consultation
  - Steroids
    - Dexamethasone for the first 48 hours may decrease the mortality rate. Study was done on severe typhoidal fever, and with the use of chloramphenicol
    - 3 mg/kg IV first dose, then 1 mg/kg Q6 for up to 48 hours
    - steroids longer than 48 hours may increase the relapse rate
  - IV Quinolone for 10 days

Typhoid Fever--Complications

- Bowel perforation
  - usually in the third week of the illness
  - Need surgical consult for peritoneal signs
  - usually ileal perforation
- Relapse occurs 5-10%, and more so with the use of chloramphenicol. Decreased relapse on quinolones

Typhoid Fever--Complications

- Chronic carrier (Typhoid Mary)
  - excretion of the organism in the stool for 12+ months
  - occurs more frequently in women with biliary abnormalities
  - 1-4% of adults with typhoid fever become carriers
  - treat with high dose Ampicillin or quinolones for up to 4 weeks
  - cholecystectomy

Typhoid Fever--Prevention

- Ensure safe drinking water, and effective sewage disposal
- Travelers should drink boiled/bottled water
  - “boil it, cook it, peel it, or fahgitaboutit”
- Wash hands!!!

- Vaccine
  - for travelers to endemic areas, household contacts of typhoid carriers, lab workers

Typhoid Fever--Prevention

- Whole cell, heat-killed or acetone-inactivated, typhoid vaccine
  - painful injection with local reaction in 25-50%
  - 65% efficacious
  - booster every 3 years
- Ty21a
  - live, attenuated oral vaccine
  - booster every 5 years
  - not for immunocompromised patients or those on ABX
  - 65% efficacy depending on the population studied

Typhoid Fever--Prevention

- Parenteral Vi based vaccine
  - booster recommended every 2 years
  - less side effects
  - knowledge of prolonged efficacy is limited, 55% over 3 years